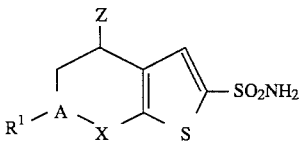
BIOCONVERSION PROCESS FOR THE SYNTHESIS OF TRANSHYDROXY SULFONE BY *RHODOTORULA RUBRA* OR *RHODOTORULA PILIMINAE*

BACKGROUND OF THE INVENTION

Glaucoma is in ocular disorder associated with elevated intraocular pressures which are too high for normal fimction and may result in irreversible loss of visual function. If untreated, glaucoma may eventually lead to blindness. Ocular hypertension, i.e., the condition of elevated intraocular pressure without optic nerve head damage or characteristic glaucomatous visual field defects, is now believed by many ophthalmologists to represent the earliest phase of glaucoma.

Compounds of structural Formula:



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the individual diastereomers, the individual enantiomers or mixtures thereof, or an ophthalmologically acceptable salt thereof, wherein:

A is carbon or nitrogen;

Z is NHR or —OR;

R is C_{1-6} alkyl, either straight or branched chain;

R^1 is

a) C_{1-5} alkyl, either straight or branched chain, especially n-propyl or isobutyl;

b) C_{3-5} alkenyl, especially allyl;

c) C_{3-5} alkynyl, especially propargyl;

d) hydrogen; or

e) C_{1-4} alkoxy-C_{1-4} alkyl; and

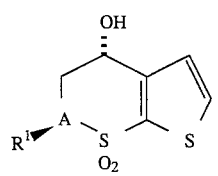
X is —SO2— or —C(O)—;

are known from U.S. Pat. Nos. 4,797,413 and 5,157,129. The compounds are known to be topically effective carbonic anhydrase inhibitors (TCAI's) useful in the treatment of ocular hypertension. The synthesis of the compounds involves the reduction of a sulfo-ketone to a trans-hydroxy sulfone precursor to the above-noted compounds. However, the synthetic processes described for their preparation result in diastereomeric or racemic products which must be separated and resolved, with concomitant loss of at least 50% of the product, to obtain the most active enantiomer.

Now with the present invention there is provided a novel microbial process for the bioconversion of the sulfo-ketone intermediate to a trans-hydroxy sulfone intermediate.

SUMMARY OF THE INVENTION

This invention is concerned with a novel microbial bioconversion process for synthesis of trans-hydroxy sulfone having the structural formula:



II

wherein A and R^1 are as described above. The trans-hydroxy

sulfone is the precursor to the final product, a carbonic anhydrase inhibitor of Formula I above. The final product is topically effective in the treatment of ocular hypertension and glaucoma. The process comprises fermentation of the sulfo-ketone substrate in the presence of the microorganism *Rhodotorula rubra*, (ATCC 74283); or *Rhodotorula pilirninae* (ATCC 32762), preferably *Rhodotorula rubra*. The biotransformation is accomplished under submerged aerobic conditions in an aqueous carbohydrate medium containing a nitrogen nutrient at a pH of about 4.5 to 8.0, preferably 6.0, for a sufficient time to produce the compound of structural formula II.

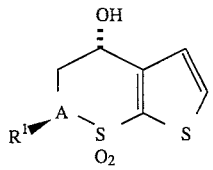
The resultant trans-hydroxy sulfone analog exhibits a diastereomeric excess of greater than 95%. The key step in this novel process, (i.e., control of the diastereomeric excess of the hydroxy sulfone), is controlling the residual sulfo-ketone concentration in the bioconversion reaction medium.

Thus it is an object of the present invention to provide a microbial process for the synthesis of the trans-hydroxy sulfone intermediate.

DETAILED DESCRIPTION OF THE INVENTION

This invention is concerned with the synthesis of the compounds of structural formula:

Trans-hydroxy sulfone-II



wherein A is carbon or nitrogen and R^1 is:

a) C_{1-5} alkyl, either straight or branched chain, especially n-propyl or isobutyl;

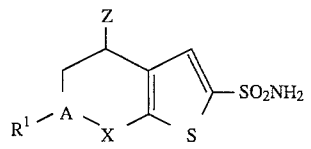
b) C_{3-5} alkenyl, especially allyl;

c) C_{3-5} alkynyl, especially propargyl;

d) hydrogen; or

e) C_{1-4} alkoxy-C_{1-4} alkyl,

which is the precursor to compounds represented by Formula:



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b) C_{3-5} alkenyl, especially allyl;

c) C_{3-5} alkynyl, especially propargyl;

d) hydrogen; or

e) C_{1-4} alkoxy-C_{1-4} alkyl; and

X is —SO_2— or —C(O)—;